EVIDENCE FOR MEDIATING ECONEUROCARDIOLOGIC MECHANISMS

CARDIAC ELECTRICAL STABILITY AND ENVIRONMENTAL STRESS  by Karen Belkić, MD, PhD

Sudden arrhythmic death is the most common mode of death among adults under the age of 65 in industrialized countries, accounting in the U.S. alone for approximately half of all CV mortality, or an estimated 250,000 to 350,000 deaths annually.21,22,27,29,32,33,36,50 Most of the arrhythmias leading to these deaths are ventricular tachyarrhythmias.26,28,31 A substantial number, in some series up to 50%, of these victims have had no previous history of known heart disease; in other words, the first cardiac episode proves to be the last.20 Bernard Lown has stated: “[Sudden cardiac death] is not the expression of inexorable and irreversible pathomorphologic alterations. It represents instead an electrical accident that can be reversed and even prevented.”21 Thus, understanding the mechanisms underlying sudden cardiac death could be of critical public health importance, particularly for primary prevention, which remains the most elusive goal.

The relation between stress and sudden cardiac death (SCD) has long been appreciated. As stated by Eliot and Buell, “History is replete with anecdotes of persons who died suddenly in the throes of intense emotion. Now scientific study is beginning to shed light on the pathways and mechanisms responsible for these observations.”47 The role of the forebrain in life-threatening arrhythmias is discussed in Chapter 4. Here, the focus is on how these processes play out on the cardiac electrical substrate. Acute and chronic stress-related factors can contribute to destabilization of the electrical substrate of the cardiac ventricle, leading to life-threatening ventricular tachyarrhythmias by a number of mechanisms.

Major Stress-Mediated Mechanisms of Cardiac Electrical Destabilization

SYMPATHETIC OVERDRIVE

Catecholamine excess is arrhythmogenic. Based primarily on laboratory studies of isolated cardiac tissues, it can be concluded that catecholamines directly evoke tachyarrhythmias by three mechanisms: (1) increased automatic activity (increased slope of phase 4 depolarization and in slow inward calcium current in partially depolarized cells), (2) augmented early and late triggering (facilitation of calcium influx),

and (3) re-entry (lowered phase 4 potential slows conduction, increases internal resistance, and diminishes cell-to-cell conduction, which promotes asynchronous repolarization. These arrhythmogenic effects have been attributed primarily to beta, but also to alpha-1 adrenergic mechanisms. Furthermore, catecholamine damage to myocardial tissue can provide a morphologic substrate for lethal arrhythmogenesis.

OTHER AUTONOMIC IMBALANCES

Unopposed sympathetic outflow is not the only stress-related mechanism by which autonomic imbalance destabilizes the heart. The balance of sympathetic outflow between the right and left stellate ganglion, as well as vagal/sympathetic ratio and its temporal relation to the cardiac cycle, are also autonomic determinants of cardiac electrical stability. Vagal outflow usually stabilizes the electrical substrate of the heart by increasing the resting potential of cardiac fibers. Low parasympathetic relative to sympathetic tone as reflected by heart rate variability (HRV) has been found on Holter recordings to precede spontaneous episodes of ventricular tachycardia. This finding provides pathophysiological corroboration for the clinical-epidemiologic association reported between altered HRV and sudden arrhythmic death.

After transmural myocardial infarction (MI), sympathetic as well as vagal efferent innervation can be compromised in noninfarcted portions of the myocardium apical to the infarct, with reduction in norepinephrine and acetylcholine concentrations. As a consequence, this denervated tissue demonstrates supersensitivity with exposure to adrenergic agents. These changes may promote cardiac electrical instability.

The temporal relations between vagal and sympathetic outflow also must be considered. Levy has demonstrated in experimental studies that varying temporal sequences of vagal and sympathetic stimulation can have disparate effects on autonomic interactions. Furthermore, abrupt withdrawal of sympathetic vasoconstrictor tone and sudden vagal outflow can lead to hemodynamic collapse as well as asystole, implicated in some animal models of sudden cardiac death, as well as clinical syndromes. The dive reflex falls into this category.

While stimulation of either stellate (sympathetic) ganglion lowers the threshold for ventricular fibrillation, the left stellate, which increases the temporal dispersion of repolarization and thereby prolongs the corrected QT interval, is twice as effective. Dynamic prolongation of the QT interval during daily activity in post-MI patients is a potential marker of risk for life-threatening ventricular arrhythmias. Exposure to sensory and/or emotional stressors, as well as physical exercise, can increase vulnerability to developing life-threatening ventricular tachyarrhythmias among patients with the idiopathic long QT syndrome.

LEFT VENTRICULAR HYPERTROPHY

Cardiac electrical stability is also jeopardized by left ventricular hypertrophy (LVH), which has a particularly close association to work-related stress. Mechanisms by which LVH may be arrhythmogenic include: (1) increased automatic activity from stretching of the myocardial fiber sheaths, (2) induction of triggered activity from disturbed calcium homeostasis, and/or (3) re-entry occurring in electrically silent areas that arise from the hypertrophied myocardium and from areas of interstitial fibrosis. Hypertensive patients with LVH have significantly greater prevalence, overall number, and severity of ventricular as well as supraventricular arrhythmias compared to those without LVH.
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MYOCARDIAL ISCHEMIA

Acute myocardial ischemia is perhaps the best recognized and most well-investigated cause of lethal tachyarrhythmias. Experimental studies reveal that the immediate effects of acute myocardial ischemia produced by abrupt coronary artery (CA) occlusion include acidosis and depletion of high-energy phosphates, leading to a loss of resting membrane potential with altered refactoriness and excitability. Conduction becomes slowed and inhomogeneous. Re-entry mechanisms appear to predominate, although automatic and triggered activity also can occur. 16,37,123,173,245 Ischemic myocardium also triggers reflex sympathetic outflow with attendant catecholamine-related arrhythmogenesis, by the above-described mechanisms. 109,239 During this early phase, lasting approximately 30 minutes, irreversible morphologic changes have still not occurred—yet mortality is high in experimental investigations. 143 This phase seems to be the correlate of very rapidly occurring death due, in the clinical setting, to primary arrhythmic events. 173,245

After about 90 minutes of coronary occlusion, lethal arrhythmias appear to arise in the interface between viable and infarcted tissue. The clinical correlate of this phase is arrhythmias that develop several hours after the onset of symptoms of acute MI. Life-threatening ventricular tachyarrhythmias also have been recorded in association with episodes of coronary artery spasm. 77,150,235,292 Animal studies reveal that lethal ventricular arrhythmias may occur during reperfusion after a short episode of CA occlusion, 114,174 especially when the occlusion was only partial, suggesting that the risk of ventricular fibrillation after CA spasm may be increased among patients with minimal CA disease. 335

The Critical Role of Higher Nervous Activity in Cardiac Electrical Stability

Mehta and colleagues point out that “despite a substantial understanding of the biochemical aspects of acute myocardial ischemia, our knowledge of which patients with acute myocardial ischemia will develop sustained ventricular tachyarrhythmias remains unclear.” 244 Superimposed exposure to acute stressors in the face of ischemic myocardium can represent the critical trigger of lethal cardiac electrical instability. Animal studies reveal that a number of stressful paradigms, such as threat of electric shock, food access denial, altered or unfamiliar laboratory environment, and avoidance task performance, significantly lower the threshold for ventricular fibrillation under conditions of experimental myocardial ischemia. It is noted that without exposure to such stressors, lethal arrhythmias rarely occurred in these animals, despite ongoing ischemia. 44,179,231,222,326 Thus, myocardial ischemia alone may not be sufficient to trigger life-threatening arrhythmias; rather, autonomic outflow may be needed in addition. 347 Stimulation of the posterior hypothalamus, which potentiates sympathetic outflow, lowers the ventricular fibrillation threshold in dogs with normal coronary arteries and, with experimentally-induced myocardial ischemia, proves to be the critical factor in the electrical stability of the heart. 221 Skinner demonstrated the role of higher cortical centers in cardiac electrical stability, using the pig model. 347 With blockade of either the frontocortical-brainstem pathways or the amygdaloid nuclei, psychologically-stressed pigs with acute myocardial ischemia were prevented from developing ventricular fibrillation.

Chemical Exposures and Cardiac Electrical Stability

Life-threatening cardiac arrhythmias and SCD can occur after a single, excessive exposure to carbon monoxide (CO) or to other substances that produce myocardial
ischemia, although low levels of CO exposure (3–5% carboxyhemoglobin) do not appear to be proarrhythmic. A number of organic solvents, especially those that are halogenated, have been shown to sensitize the myocardium to catecholamine and thereby compromise the heart’s electrical stability. Fatal outcomes after heavy exposure to these substances have been reported in the industrial setting. Acute re-exposure to nitrate esters, notably ethylene glycol dinitrate, among workers in the explosives industry has been associated with sudden cardiac death. There are numerous reports of these deaths occurring upon return to work after a brief period of absence from dynamite manufacturing work: “Monday Morning Sudden Cardiac Death.”

**Monday Morning Sudden Cardiac Death**

The over-representation of SCD and other acute cardiac events in the early morning hours of Mondays may not be limited to workers in the explosives industry. There is substantial data demonstrating a circadian variation in SCD and MI, with a peak in the morning hours after waking. A number of the preconditions for plaque rupture and thrombus formation are present at that time of day. In the morning hours after waking, systolic blood pressure increases by about 20–30 mmHg, heart rate and vascular tone rise, platelets are hyper-reactive, and fibrinolytic activity is at its low. Sympathetic activation occurs upon assuming the upright position, and in the early morning cortisol is at its peak. This can result in a glucocorticoid-related increase in coronary-artery sensitivity to catecholamine-mediated vasoconstriction. Beta-adrenergic blockade is found to attenuate this early morning peak in SCD. Willich and colleagues point out that besides assuming the upright posture, other morning activities may trigger an increase in sympathetic outflow.

A weekly variation in the occurrence of acute MI with a peak on Mondays has been reported among patients who had been working, but not in those who were not employed at the time of MI. In that series a similar trend was not observed, however, for SCD. In contrast, among a cohort study of 3983 men without manifest IHD, an excess proportion of sudden cardiac deaths, but not MI or cancer deaths, was found on Mondays.

Epidemiologic studies of unmonitored, out-of-hospital SCD are fraught with methodologic difficulties; death certificates lack both sensitivity and specificity; and major definitional dilemmas still exist. Sudden death at work has been underestimated by death certificates. An investigation of coroners’ reports reveals an annual, age-adjusted rate of sudden death at work twice that of fatal work injuries. Systematic examination of the incidence of life-threatening ventricular tachyarrhythmias among 683 patients with third-generation automatic implantable cardioverter defibrillators (AICD) reveals a highly significant septidial distribution of these arrhythmias, with the largest percentage (21%) of AICD activations occurring on Mondays, twice greater than the number of episodes during the weekend. Employment data was not available on these patients.

These epidemiologic findings along with the biological data render plausible the conclusions that “the stress of work after a weekend of respite may have been the precipitant of a lethal arrhythmia” and that “an increase in physical and mental burden from leisurely weekend activities to stressful work on Monday in the majority of working patients” is causally related to the occurrence of acute MI.
MECHANISMS LEADING TO HYPERTENSION AND CV MORBIDITY by Joseph Schwartz, PhD, Karen Belkić, MD, PhD, Peter Schnall, MD, and Thomas Pickering, MD, DPhil

The relationship between elevations in blood pressure (BP) and cardiovascular risk is “strong, continuous, graded, consistent, independent, predictive, and etiologically significant for those with and without CHD.”7 From the age of 20 on, in the U.S. and other industrialized settings, BP increases progressively with age for the population as a whole, so that by age 60 approximately 50% of the population has hypertension, according to the standard definition of BP > 140/90 mmHg.252 It is now clear that an increase in BP, even for those at a far lower level of BP than the current definition of hypertension, is associated with an increase in CHD risk.7 With heart disease and stroke representing the first and third leading causes of death in the U.S., respectively, the public health implications of the hypertension epidemic are clear.253

Essential hypertension is a chronic disease process defined by the presence of persistently elevated (not just acutely elevated) BP, without secondary causes. Epidemiologic evidence reveals that essential hypertension is a disease of industrialized society, as there is a minimal hypertension disease burden among hunter-gatherers, nonmarket agricultural communities, and other nonindustrialized societies.29,317 Within industrial society, hypertension is socially patterned by class, race, and gender.137,294,192

Current evidence suggests that the “unidentified” cause(s) of essential hypertension most likely include one or more ubiquitous exposures. Thus, diet, lifestyle, work, and community should be examined. An adequate explanatory risk factor would also have to be consistent with the above-mentioned social patterning of the disease. Migration studies strongly suggest that genetic factors are not the primary determinants of hypertension. This is dramatically demonstrated by the fact that African-Americans have among the highest rates of hypertension in the world, whereas in rural West Africa (from whence African-Americans underwent forced migration to the U.S.) the prevalence of hypertension is among the lowest in the world.59

The contemporary work environment is a ubiquitous environmental exposure. It is the locus in which adults now spend the majority of their waking time. The work environment is frequently the source of exposures to psychosocial, physical, and other cardionxious factors.

We know that BP is higher during working hours, compared to leisure time, within a 24-hour period.328 Furthermore, mean 24-hour BPs are lower on nonwork days compared to work days.286 These observations have been made possible by the development of ambulatory blood pressure (AmBP) devices, and their use in working populations. In comparison to casual clinic BP, AmBP is a better reflection of “true blood pressure” and has been demonstrated to be superior to the former in predicting target organ damage (such as left ventricular hypertrophy) and clinical prognosis.8,277,279,383 Thus, studies using AmBP provide indispensable insights into the link between environmental/situational factors and hypertension.

Whether, how, and when repeated acute rises in BP transform into the chronic process of essential hypertension are only partially understood. Clearly, longitudinal studies that follow this process over time are critical to our understanding of the mechanisms involved. Our goal is to present the current biological models and existing empirical evidence, to identify where the argument of biological plausibility is best substantiated.
Workplace Stressors and Hypertension

Occupations at High Risk

A number of the occupational groups that are at high risk for developing ischemic heart disease (IHD) also show an elevated risk for hypertension and/or elevated resting BP. These include professional drivers,1642,25,297,408 air traffic controllers,57 and sea pilots.59 These occupations can be characterized as predominantly threat-avoidant vigilant jobs, with a high total burden of occupational stressors. Cumulative exposure to this occupational stress burden emerges as a significant, independent predictor of hypertension among urban transit operators.298 Among San Francisco urban transit operators aged 45–54 with over 20 years on the job, 52.2% had hypertension. In comparison, the prevalence of hypertension was 42.9% among those of the same age strata who had been on the job less than 10 years, and 48.8% among those with 10–20 years on the job. Prior to employment as an urban transport operator, the prevalence of hypertension among a group of the same age was 36.7%.

Elevations in AmBP have been found during working hours among urban transport operators, compared to workers whose overall occupational stress burden is much lower.397 Acute rises in AmBP have been observed during emergency situations among healthy, middle-aged train drivers whose BP increased by +12.7/+9.4 mmHg compared to resting values.154

Chronic Exposure to Job Strain and Effort-Reward Imbalance

Of the psychosocial work stress models relevant to cardiovascular disease (CVD), the Job Strain Model has been one of the most intensively investigated in relation to hypertension. Strong empirical evidence links exposure to job strain with elevations in AmBP, greatest at work but also evident at home and during sleep. Besides the consistent body of cross-sectional data in men and women and the demonstration of a dose-response relationship, recent longitudinal studies reveal a significant cumulative effect, as well.201,225 In the Cornell Work Site Blood Pressure Study, the adjusted worktime AmBP of men who were exposed to job strain at baseline as well as 3 years later was greater by 11.1/9.1 mmHg, compared to those without exposure at either time.322 Exposure to high effort together with low rewards at work also has been demonstrated to predict hypertensive status prevalence in combination with hyperlipidemia.341,343

Physical and Chemical Exposures

Empirical evidence links exposures to certain physical and chemical agents with hypertension. With regard to noise, the literature is abundant, but not entirely consistent. However, several fairly recent studies were positive.76,90,251,365 and three of these took into account length of exposure.76,231,365 In the study of Talbott, et al., cumulative occupational noise exposure was a significant independent predictor of systolic BP in the two plants studied, while it predicted diastolic BP in only one of the plants.365 The authors attribute this latter finding to a possible threshold effect. Among male industrial workers aged 25–44 with normal BP, Green and colleagues found a +3.2/+2.3 mmHg effect on work AmBP among those exposed to > 85 dB noise (p < 0.001), after controlling for potential confounders.120 No significant effect was seen among those over 44 years of age. However, in another study from the same center in Israel, work AmBP was not significantly associated with noise intensity among male or female blue-collar workers.105 Some evidence suggests that exposure to lead or to arsenic may be associated with an increased risk of hypertension.21,149
LONG WORK HOURS AND SHIFTWORK

Studies by Hayashi, et al.\textsuperscript{136} and by Iwasaki, et al.\textsuperscript{159} have shown that long working hours are associated with elevations in AmbP as well as usual BP. Shift workers appear to reverse the usual circadian BP pattern, showing peak levels at night while working. Chatu and colleagues found that while the mean BP during the high pressure span was the same for three shift schedules, the duration of the high pressure span was longest during the night shift, and shortest during the afternoon shift.\textsuperscript{59} There is also evidence that shift workers' BP during sleep fails to drop to the levels seen among day workers. In a study of approximately 100 nonhypertensive nurses, Yamasaki, et al. showed that those who worked evening/night shifts had higher BP during sleep than those who worked day shift.\textsuperscript{49}\textsuperscript{4} As a result, shift workers exhibited less "nocturnal dipping," the lack of which has been associated with increased left ventricular mass according to Verdecchia, et al.,\textsuperscript{34} although not according to Bhatt, et al.\textsuperscript{30} A recent longitudinal study by Morikawa and colleagues indicates that among young (<30 y.o.), initially normotensive, blue-collar working men in a single factory, the relative risk of developing hypertension during the 5-year followup was 3.6 for those who rotated shifts compared to those who worked day shift only, after adjusting for age, BMI, alcohol intake, and baseline systolic BP.\textsuperscript{25} This effect was not seen among older workers, however.

Human Blood Pressure Responses to Simulated Work Stressors

ECOLOGICAL RELEVANCE

A large body of research examines human CV responses to various stressful paradigms. While acute elevations of BP and heart rate are achieved, these paradigms often bear little or no resemblance to real aspects of working life. Besides the artificiality of the laboratory environment itself, the tasks have not usually been chosen for their similarity to the cognitive exigencies of the subjects' jobs. Very few studies have, by design, examined between-subject responses to laboratory stressors that are similar to the subjects' workplace exposure. It is therefore not surprising that many of these studies have failed to find that BP reactions to laboratory stressors reflect real-life BPs during a workday.\textsuperscript{121,287,352} Pickering concludes that "viewed as a whole, these studies suggest that if there is an association between reactivity measured in the laboratory and the BP variability or reactivity of daily life, it is rather weak, or is obscured by the problems of measurement error."\textsuperscript{287}

Pickering notes, however, that when the laboratory stressors closely resemble task performance during real life, a significant correlation in BP responses has been found. He cites a study by Matthews, et al., in which BP changes during a laboratory speaking task were compared to a similar task in the classroom.\textsuperscript{328} Concordantly, Steptoe and Vögele emphasize the importance of "ecological validity" of laboratory mental stress tests, which should be designed "to model processes that will be important to CV health only if they are repeated or sustained in everyday life over many years."\textsuperscript{352}

BP response during an interview in which stressful workplace events are discussed can be informative, precisely because of the personal relevance of the subject. For example, among 22 young, healthy, mainly blue-collar, male workers, a short semi-structured laboratory interview about intensely stressful events related to work (e.g., work accidents, interpersonal conflicts) produced a greater pressor response (+12.4/+15.1 mmHg) than any of the standardized mental stress tests, (mental arithmetic, quiz, auditory and visual choice-reaction time tasks).\textsuperscript{19}
MENTAL STRESS

A body of laboratory-based cardiovascular research provides insight into some of the more generic aspects of workplace mental stress, most notably job strain. For example, external pacing, an important component of low control during performance of mental arithmetic is associated with increased systolic and diastolic BP responses. Peters and colleagues found that both increasing effort in a mental task and lowered control provoked elevations in BP and plasma norepinephrine. Uncontrollability also was associated with elevations in salivary cortisol. Furthermore, an effort-control interaction effect was observed with respect to diastolic BP response. Steptoe and colleagues found that BP reactions to an externally paced (low control) task were greater in teachers with high as compared to low job strain. In contrast, BP responses to a self-paced (high control) task did not differ significantly between these two groups.

The ameliorating effects of social support also have been demonstrated in the laboratory setting. During performance of a speech task, BP reactivity was attenuated when an audience observer behaved in a supportive manner (nodding and smiling) as compared to acting neutrally.

PHYSICAL STRESS

One ecologically valid, laboratory-based model of a work-related physical stressor is the glare pressor test (GPT), in which a standardized stimulus mimics the commonly occurring circumstance of facing an oncoming headlight during night driving. Studies using the GPT were designed to compare exposed groups (professional drivers) to those with no driving experience whatsoever. Compared to matched working non-driver referents, young normotensive professional drivers showed diastolic hyperreactivity to the GPT, together with digital vasoconstriction and signs of central arousal (EEG desynchronization). It has been postulated that BP reactivity to the GPT represents an early phase of sensitization (a conditioned defense response) to threatening stimuli in the driving environment which, with continued exposure, may lead to sustained hypertension. Longitudinal study is needed to further test this hypothesis.

Some laboratory paradigms of noise exposure have provoked significant elevations in BP, while others have not. Among 18 healthy males, 95 dB of industrial noise induced significant elevation in diastolic BP, which persisted during the 20-minute exposure period. Total peripheral resistance (TPR) increased significantly, while stroke volume and cardiac output fell. Sawada also found an increase in TPR, together with a reproducible, persistent elevation in BP, when a similar group of subjects was exposed to 100 dB of pink noise. A significant elevation in systolic BP associated with noise exposure during performance of mental arithmetic has been reported by Linden, but not by Tafalla and Evans.

The cold pressor test (immersion of the hand into cold water for 1–3 minutes) induces significant increases in systolic and diastolic BP and marked elevations in norepinephrine and epinephrine levels. Several studies applying the cold pressor test found no relation between reactivity and future level of BP. The study of Menkes, et al., however, revealed that even after statistically controlling for other risk factors, including family history of hypertension, hyperreactivity to the cold pressor test was a significant predictor of hypertension among 1000 medical students followed for 20–36 years.

Isometric handgrip is also an extremely potent pressor stimulus. Both systolic and diastolic BP rise out of phase with heart rate, and the baroreceptor set point is
changed such that a disproportionate pressure load is placed on the heart. Neurogenic mechanisms along with local factors such as afferent reflex stimulation and mechanical hindrance to blood flow, contribute strongly to these cardiovascular changes. In normal subjects, isometric handgrip to one-third maximal capacity for 3 minutes evoked the greatest diastolic BP rise of a series of ten powerful cardiovascular stressors. It also was associated with a significant rise in norepinephrine and epinephrine. Among borderline hypertensive men, mean peak BP during isometric handgrip was 181.8/114.9 mmHg. At 1-year followup BP reactivity while performing isometric handgrip and mental arithmetic was significantly correlated with the risk of developing established hypertension, but this association became nonsignificant after controlling for basal diastolic BP and mean ambulatory systolic BP during the day.

Among 33 post-MI patients, carrying graded loads of 20–50 lbs. while walking on a treadmill was associated with diastolic BP levels > 120 mmHg. Hietanen reported that static exercise training (e.g., weight lifting, hammer throwing) was associated with increased ventricular wall thickness, and noted that increased afterload is the physiologic adaptation to static exercise (as opposed to increased pre-load for dynamic exercise).

Thus, a number of physical stressors can provoke substantial acute rises in BP. However, the relationship between acute BP changes to these stimuli in the laboratory and tonic BP elevations brought about by chronic occupational exposure needs exploration.

**Biological Mechanisms: I. The Defense Response**

**The Acute Reaction: Preparation for “Fight or Flight”**

The defense response comes into play when the organism is called upon to actively cope with a threat or challenge. The cardiovascular system is geared up for the anticipated physical activity (fighting or fleeing): cardiac output increases, with blood flow directed to the heart, brain, and skeletal muscle at the expense of the viscera. Skeletal muscle vasoconstriction ensues, as a result of CNS inhibition of vasoconstrictor activity to skeletal muscle fibers and circulating epinephrine binding to beta-2 receptors in muscle resistance vessels. Higher CNS centers inhibit baroreceptor vagal activity, such that heart rate is simultaneously elevated. Efferent renal sympathetic nerves increase their firing, leading to diminished renal blood flow; the renin-angiotensin system activates; the glomerular filtration rate falls; sodium retention is enhanced; and blood volume increases. The net hemodynamic result of activating the defense response is a rise in BP, with a hyperkinetic heart and with total peripheral resistance (TPR) usually within normal levels, although TPR is high relative to cardiac output. The defense reaction to an acute threat is a rapid-acting, and arguably the best understood, biological mechanism for regulating BP and heart rate. The release of catecholamines triggered by the sympathetic nervous system produces nearly instantaneous increases in BP and heart rate, increasing the supply of oxygen and energy to the musculoskeletal system so as to facilitate active physical responses to environmental challenges.

**Relation of the Defense Response to Sustained Hypertension**

The defense reaction is phylogenetically a very old response and is adaptive when the challenges faced by the organism are primarily direct, calling for a physical response. Levi notes that this reaction was "of practical value to Stone Age people confronted by a pack of wolves... (but that) we still prepare for bodily activity and muscular exertion when we encounter changes in our environment and the demands for adjustment that
they imply. Our environment—most of all, our work environment—however, has undergone drastic changes over the millennia. The demands placed on our adaptability have altered in character, while our genes have hardly changed.\textsuperscript{212}

Gilmore in paraphrasing Charvat, Dell, Folkow, and Folkow\textsuperscript{48} graphically illustrates this point as follows:

\textit{When a gazelle hears a predator approaching cardiovascular and humoral changes develop immediately, while the somatomotor or muscular response is perhaps only an alerting reaction. Later, as the predator comes closer, the gazelle explodes into an all-out flight response, with his cardiovascular system being already prepared.}

\textit{In contrast, civilized man is faced with stress-producing situations (which) seldom relate to physical danger, such that the defense response is no longer well coordinated, the autonomic-humoral component being dissociated from the somatotropic or muscular response. Since the cardiovascular or metabolic resources intended to support heavy or violent physical exertion will not be utilized in the natural way, the hormonally produced changes of the blood, and thus, the chemical environment of the blood vessels and the heart will be more long-lasting than when violent muscular activity occurs. In addition, since the neurogenically induced cardiovascular changes are not modified by the additional vasodilatation due to muscular activity itself, the pressure load on the heart and blood vessels will be greater than if muscular activity occurred.}\textsuperscript{122}

The idea that intermittent elevations of BP, occurring in response to repeated exposure to environmental stressors and elicitation of the defense response, could result in sustained hypertension was first proposed by Folkow.\textsuperscript{94,95} Folkow notes that when physical activity is suppressed, the magnitude of the pressor response to sympathetic activation becomes greater because there is no exercise-induced muscle vasodilatation. This is seen as a “forced dissociation of normal response patterns,”\textsuperscript{97} which Elliot has described as a “constant state of visceral-vascular readiness,”\textsuperscript{96} whereby the heart and blood vessels are activated irrespective of the actual metabolic needs of the organism. Thus, while the defense reaction, including the acute elevation in BP, is adaptive in the short run under certain circumstances, it may be maladaptive in the long run.

Still unknown are the precise dynamics by which repeated evocation of the defense reaction without physical fight-or-flight behavior translates into sustained hypertension. Elevations in BP do not necessarily lead to hypertension. As shown by Julius, et al., mechanical compression of the thighs in dogs can produce an acute increase of BP for as long as the compression is applied, but without causing any upward drift of the resting pressure.\textsuperscript{169} Chronic instrumental CV conditioning in nonhuman primates provokes repeated elevations in BP, but does not consistently evolve into sustained hypertension after the conditioning paradigm is discontinued.\textsuperscript{377} Heary and colleagues have found that long-term social disruption leads to hypertension in some but not all initially normotensive rats.\textsuperscript{141} While heart and adrenal weights, adrenal catecholamine synthetic enzymes, and pathohistologic changes in the heart, aorta, and kidney in several rat strains generally paralleled the BP changes, the Wistar-Kyoto hyperactive strain showed stress-induced increases in heart and adrenal weights, but no BP changes. Thus, many questions are unanswered. The length and intensity of exposure to the stressor, and its nature, clearly are issues of importance.
THE ROLE OF ADRENERGIC ACTIVITY IN THE EARLY STAGES OF HYPERTENSION

BP changes occur over various time frames, and the factors that cause acute changes may not be the same as those that contribute to chronic changes. The fluctuations that occur throughout the day in response to environmental circumstances have been collectively called the "phasic" component of BP; the "tonic" (long-term resting level) component changes only gradually over time.285 Essential hypertension is defined as an elevation of the tonic component.

There is evidence of a subtle increase in the level of sympathetic nervous system (SNS) activity in many patients during the early stages of hypertension, and this increase is primarily tonic rather than phasic. For example, several (but not all) studies have demonstrated that subjects with mild hypertension have increased resting catecholamine excretion, heart rate, and cardiac output,124,165,283 as well as enhanced catecholamine responses to stressors.152 Oparil and colleagues review a number of lines of evidence implicating SNS activity in essential hypertension. They state that "SNS activity is elevated in nearly every form of human and experimental hypertension, and reduction of this activity decreases arterial pressure" and note that "chemical or surgical lesions of the SNS lower arterial pressure in most hypertensive individuals."270 Concordant conclusions are drawn by Mancia, particularly focusing on direct measurement of sympathetic nerve traffic to skeletal muscle circulation, which is found to increase with progressively more severe degrees of essential (but not secondary) hypertension.231

Pharmacologic studies, predominantly conducted by Majewski and Rand, have identified one potential mechanism by which adrenaline (epinephrine) might mediate stress-linked hypertension.228 Both in vitro and in vivo studies have shown that infusion of epinephrine in low doses (equivalent to the levels seen during naturally occurring stress) can enhance norepinephrine release from sympathetic nerve terminals.228 Although sustained experimental neurogenic hypertension has been quite hard to produce in practice, Majewski, et al. achieved it in rats using a slow-release depot implantation of epinephrine.259 After the 8th week, when excess epinephrine could no longer be detected in the plasma, BP (but not heart rate) was still elevated.

Similarly, Blankenstijn, et al. showed that the arterial pressure of humans infused with epinephrine was at first reduced, but by the end of the infusion (6 hrs) was above the baseline value, and remained elevated throughout the night.31 The pressor effect of epinephrine was most marked during periods of increased sympathetic activity—for example, when the subjects were active—and not when they were at rest. Infusion of norepinephrine produced an initial elevation of pressure, but no sustained effects.

STRUCTURAL CHANGES IN RESISTANCE VESSELS

Through repeated elicitation of the defense reaction—i.e., repeated pressor episodes—structural changes may gradually occur in the cardiovascular system, and these can result in a higher basal BP. Adrenergic neurotransmitters and other substances (e.g., angiotensin and insulin) that rise in association with the defense response act as "growth promoters" on vascular smooth muscle.172 Prolonged exposure of resistance vessels to these substances can result in vascular structural changes (hypertrophy) and increased smooth muscle contractility. This is precisely what occurs during repeated exposure to mental stress, due to the lack of skeletal muscle vasodilatation. Furthermore, mechanical factors related to increased wall pressure, tension, or stress promote increased vessel wall thickness.265
According to Folkow and colleagues, activation of smooth muscle during repeated exposure to acute stress, even if only intermittent, can stimulate an increase in smooth muscle cell size (hypertrophy), thereby increasing the wall thickness of the resistance vessels and shrinking their internal radius. The net result is an increase in peripheral resistance. These hypertrophied vessels are rendered hyper-responsive to vasoconstrictive stimuli. This could explain why stress responses of hypertensive individuals are predominantly characterized by vasoconstriction with elevation of TPR, while the response of normotensive individuals is usually an increase in cardiac output. Egan and colleagues have demonstrated increased forearm vascular resistance responses to norepinephrine and angiotensin II in patients with mild hypertension, compared to weight-matched normotensive controls. The net outcome is a chronically increased TPR, usually with a down-regulation of beta-adrenergic receptors in the heart, leading to a normal cardiac output, as seen in established hypertension.

RENAI MECHANISMS AND LONGER-TERM CHANGES IN ARTERIAL BP

Besides structural changes in resistance vessels, longer-term changes in arterial BP appear to be strongly influenced by renal mechanisms. Guyton provides a possible explanation of how neurogenic mechanisms could contribute to chronic hypertension by their effects on the kidney. With SNS activation, the renal vasculature becomes severely constricted, compromising renal blood flow. For example, chronic infusion of norepinephrine can permanently damage the renal arteries. Severe essential hypertension is characterized by approximately half the normal renal blood flow and a two- to fourfold increase in renal vascular resistance. In order to maintain an adequate glomerular filtration rate, the arterial pressure must be maintained at a high level. Furthermore, there is evidence that environmental stress can cause sodium retention, mediated via renal sympathetic nerve activity in animals and in humans. Hollenberg, et al. showed that the effects on renal blood flow of a behavioral challenge lasted much longer than the effects on BP. This, in turn, can lead to sodium retention and a gradual increase in tonic BP.

Increased salt intake may exacerbate this process. Poulter and Sever present a model by which neurogenic pressor mechanisms (repeated elicitation of the defense response) combined with increased dietary sodium may together account for the elevated BP among persons migrating from environments with a low to those with a higher prevalence of hypertension. However, Waldron and colleagues reported that the higher BPs that developed in the latter settings (e.g., those affected by the market economy, economic competition, breakdown of family ties) appeared to be independent of salt intake.

FURTHER INSIGHTS FROM PSYCHOSOCIAL STRESS MODELS IN ANIMALS

Henry notes that in the early stages of psychosocial stimulation (continuing conflict resulting in social instability) in mice, adrenal catecholamine synthetic enzymes approximately double, and plasma renin is very high. After about 3 weeks, however, although systolic BP is elevated, plasma renin levels have fallen. Subsequently, the renal and hindquarter vessels show greatly enhanced sensitivity to angiotensin. Induction of hypertension in experimental animals requires several months of repeated exposure to stressful situations. These experimental results provide a biological rationale for the finding that an induction period appears to exist before exposure to job strain gives rise to an increased risk of established hypertension.
WORK STRESSORS, DEFENSE RESPONSES, AND HYPERTENSION: IS THERE A LINK?

The threats and challenges of working life are clearly capable of provoking arousal, as characterized by the defense response. Because these threats and challenges are often of a chronic nature, and are rarely, if ever, resolved by a physical fight-or-flight reaction, a prolonged state of "visceral-vascular readiness" is likely to emerge. Elevations in catecholamine excretion, typical of the defense response, have been associated with exposure to numerous acute and chronic work stressors. Furthermore, elevations in BP and catecholamine excretion during stressful work appear to be related. Among women who perceived work as the greatest source of stress, systolic BP at work was significantly higher compared to women who cited home as the greater stressor. In the former group, the percent changes in BP and catecholamine excretion during waking hours (relative to sleep) were significantly correlated. In contrast, among the women who cited home as more stressful, these waking BP changes were not correlated with changes in urinary catecholamines.\(^{16}\)

Studies among professional drivers have demonstrated that laboratory stressors that are reminiscent of the threats and challenges of the work environment elicit signs of electrocortical arousal characteristic of the defense response, especially in hypertensive transport operators.\(^ {85}\) Other studies in which ecologically valid work stressors have been simulated in the laboratory indicate that these are capable of eliciting significant acute BP elevations.

However, Schwartz, Pickering, and Landsberger note that for work stress to contribute to a tonic elevation in BP, "the blood pressure of the exposed individuals would have to be elevated not only in the presence of a stressor but also during rest."\(^{32}\) Thus, the focus should be on "exposure to chronic low- or moderate-grade stress rather than on discrete events that are widely acknowledged to produce brief spikes in the blood pressure profile."\(^{12}\) The large, consistent body of data on AmbP and exposure to job strain indicates that these elevations are indeed persistent. They occur not only at work, but also at home and, in some studies, during sleep. Finally, and probably most compelling, are the data indicating that there may be a cumulative effect of chronic exposure to job strain on AmbP.

Biological Mechanisms: II. The Defeat Reaction and Glucocorticoids

Although most attention has been paid to the SNS as the prime mediator of stress-induced increases in BP, evidence also suggests that activation of the hypothalamic-pituitary-adrenocortical (HPA) axis may be involved. During exposure to some acute stressors, particularly those that are psychologically threatening (e.g., public speaking), cortisol is released over a period of about 15–20 minutes. This release is much more gradual, but also persists much longer after termination of the stress condition, than that of epinephrine and norepinephrine.\(^ {180}\)

Animal studies reveal that when repeatedly faced with noxious events that cannot be controlled, motivation becomes undermined, resulting in passive behavior and giving-up. In animals this pattern has been labeled the "defeat reaction,"\(^ {142}\) while in humans it is perhaps most closely linked to the construct of learned helplessness.\(^ {351}\) According to Folkow, defeat reactions, if prolonged, "may exert more harmful effects than strong and prolonged defense reactions."\(^ {70}\) Defeat reactions tend to activate the HPA axis to release glucocorticoids. Glucocorticoids have a likely pressor role, both singly and as potentiators of reactivity to adrenergic and angiotensin II stimulation.\(^ {352, 270, 312, 324}\) They also have a weak mineralocorticoid effect, leading to renal sodium reabsorption at higher doses.\(^ {355}\) Thus, it is possible that glucocorticoids play a major role in mediating the effects of chronic stress.
Experimental studies have shown that strong control over an animal’s behavior provokes hypertensive responses. An integrated CNS–behavioral stress response pattern, distinct from the defense response and characterized by passive behavior (motoric immobilization, lying still, “playing dead”), generalized vasoconstriction, and vagally mediated bradycardia has been identified. This “defeat-type” reaction pattern is typical of the “dive reflex,” and can be activated under conditions of hopelessness, extreme fear, or exhaustion. A similar pattern also has been evoked by stimulation of the lateral hypothalamus in rabbits. Finally, short-lived, repeated stimulation of the lateral hypothalamus for several days to weeks in rats leads to a progressive, sustained rise in arterial BP. The role of the HPA axis in these processes needs to be further investigated.

**Chronic Defeat Reactions and Hypertension**

While pointing out the pitfalls of extrapolating from animal or human laboratory studies to real life, Lennerlöf hypothesized that “jobs that are characterized by little control, influence, learning and development entail risks of hopelessness learning.” Some empirical support for this hypothesis comes from the Cornell Work Site Blood Pressure Study (WSBPS), in which Landsbergis and colleagues examined questionnaire responses of participants whose jobs were characterized as passive, i.e., low control, but also low demand. These workers’ responses to Seligman’s Attributional Style Questionnaire indicated high levels of learned helplessness. Kohn and Schooler reported similar findings concerning the relationship between job characteristics and personality, both cross-sectionally and longitudinally. However, contrary to expectation, the WSBPS participants in passive jobs did not show any elevation in BP compared to those in jobs with low demand and high control or high demand and high control.

Empirical data links both acute (e.g., traffic peaks during bus driving) and chronic (e.g., heavy psychosocial job burden) exposure to work stressors with elevations in cortisol. There is also some evidence that low job control is associated with elevated BP. For example, having undergone a forced job change was found to be a significant predictor, cross-sectionally, of hypertension among middle managers. In a study by Hrenstam and Theorell, low skill discretion predicted systolic AmBP among prison guards. The meta-analysis of Pieper, et al. reported a significant association between low job decision-latitude and casual systolic BP. However, there are also a number of studies in which low control, as a main effect, failed to show any association with BP. These include the AmBP studies of Light, et al. as well as several casual BP studies, including the prospective investigation of Siegrist. The outcome measure in the latter study was the co-occurrence of hypertension and hyperlipidemia (see Chapter 2 for further details). No single study has yet investigated each of the links in the hypothesized defeat reaction model as it applies to work stress and BP: low control → defeat reaction/learned helplessness → increased HPA axis activation → increased BP.

**Biological Mechanisms: III. The Effort-Distress Model**

Folkow states, “the ancient ‘defense’ and ‘defeat’ reactions, intended for quite different situations, are often activated by the artificial stimuli and symbolic threats inherent in today’s hectic and competitive life. . . . when intensely engaged over longer periods they can, indeed, profoundly disturb inner organ systems and metabolic events.” He notes that in stressful situations there often are shifts between the defense and defeat reactions. Activation of both the sympathoadrenal medullary and the HPA cortical axes can be seen in such situations. Frankenhaeuser observed
that the activation of these two axes could be evoked in human laboratory studies by paradigms that demanded effort while providing little or no opportunity for control over the task performance, a condition she hypothesized would engender distress.104 This led to the Effort-Distress Model, which was described as follows:

Effort with distress is probably the state most typical of our daily hassles. It is accompanied by an increase in both catecholamine and cortisol secretion. Most of our studies concern this category. For instance, mental work carried out under conditions of either stimulus underload or overload will typically evoke feelings of effort, as well as distress and, consequently, both the catecholamine and the cortisol level will rise. . . . The key question is how to achieve the state of effort without distress. Our data point to personal control as an important modulating factor in this regard. A lack of control is almost invariably associated with feelings of distress, whereas being in control may prevent a person from experiencing distress. Hence, personal control tends to act as a buffer, reducing the negative arousal effects, and thereby changing the balance between sympathetic-adrenal and pituitary-adrenal activity.104

One of the experimental paradigms applied in this context was performance of a monotonous vigilance task, as compared to a self-paced, reaction-time task. Both conditions required similar effort, but the former was associated with distress, while the latter was primarily enjoyable. During the vigilance task, both epinephrine and cortisol increased, whereas during the reaction-time task only epinephrine rose.226 In a more recent study, Peters and colleagues applied a similar paradigm and registered BP as well as hormonal responses.281 They found that when the effort involved in laboratory task performance increases and control is simultaneously diminished, not only do both catecholamines and cortisol rise together with BP, but an effort-control interaction effect is observed with respect to diastolic BP responses.

The Effort-Distress Model has not been tested as a predictor of sustained hypertension.299 It mainly has been applied in the human laboratory setting. However, neuroendocrine changes consistent with activation of both the sympathetic-adrenomedullary and the HPA axes have been demonstrated among metallurgists when performing paced assembly work with no control over the work pace.298 These working conditions are clearly typical of job strain. The distress condition of the Effort-Distress Model is conceptually very similar to the high-strain condition of the Job Strain Model, though they are typically used to characterize laboratory versus actual workplace situations, respectively. While there is strong empirical evidence that chronic exposure to job strain is associated with the development of sustained hypertension, more investigation is needed to ascertain whether a combined catecholamine-glucocorticoid effect represents a major mechanism by which this process occurs.

**Work Stress and Left Ventricular Hypertrophy**

Schwartz, Pickering, and Landsbergis suggested that occupational stress may be of special etiologic importance in the progression from hypertension to IHD.329 One of the mediating mechanisms may be increases in left ventricular mass (LVM), which is a major risk factor, independent of BP, for MI, cardiac electrical instability, and sudden cardiac death.25,113,514,646,320

Devereux and Roman contend that increased LVM occurs as a direct effect of chronic elevations in BP, due to increases in stroke volume together with impairment of myocardial contractile performance.79 In contrast, Mancia argues that SNS activation is also crucial,231 citing data indicating that increased LVM can be induced by
sub-pressor doses of adrenergic agents, and that lowering BP in spontaneously hypertensive rats prevents increased LVM only if not accompanied by high reflex sympathetic outflow to the heart. Occupational stress can provoke both the hemodynamic and the adrenergic changes that promote increased LVM.

Ambulatory BP has been found to be more predictive of LVM or wall thickness than casual BP. LVM is more highly correlated with average BP at work than at other periods, but a strong relation also has been observed between LVM and home BP measured on workdays. Devereux and Roman interpret these findings as an indication of a “special impact on the heart of blood pressure responses to regularly recurring stress at work, with possible ‘spillover’ effect of home blood pressures on working days.” In addition, Schnall and colleagues found that exposure to job strain is associated with increased LVM index. Synthesizing these results, we hypothesize that long-term exposure to job strain leads to a sustained elevation of BP that then causes structural changes in the left ventricle. Considering the strong, independent relation between increased LVM and cardiovascular morbidity, this pathophysiologic process may account for a substantial part of the reported association between job strain and CHD morbidity.

**MYOCARDIAL OXYGEN SUPPLY AND DEMAND: ENVIRONMENTAL TRIGGERS OF IMBALANCE**

*by Karen Belkić, MD, PhD*

Whether or not accompanied by symptoms, myocardial ischemia has major prognostic importance. It is the consequence of an imbalance between the oxygen demand made by the myocardium and the available O₂ supply. Determinants of myocardial O₂ demand include: heart rate, blood pressure, myocardial contractility, size of the left ventricle (LV), and the duration of systole. Supply of O₂ to the myocardium is determined by coronary artery blood flow, the intraluminal size of the coronary arteries, the O₂ content of hemoglobin, the duration of diastole (during which approximately 85% of the coronary blood flow occurs), and coronary perfusion pressure (the difference between arterial pressure at the aortic root level and LV filling pressure). Many of these determinants of myocardial O₂ supply and demand are affected by stress mechanisms and/or by chemical and other physical factors in the work environment. Exposure to these stressors has induced signs of myocardial ischemia among persons with various stable ischemic syndromes, and, in some instances, among apparently healthy workers.

**Laboratory Studies of Mental Stress and Myocardial Ischemia**

Laboratory studies have demonstrated that mental stress can trigger myocardial ischemia in 40–70% of patients with various stable ischemic syndromes. This is specifically associated with an adverse prognosis. Among patients with single- or multiple-vessel coronary artery disease (CAD) LV ejection fraction assessed by radionuclide ventriculography as an indicator of myocardial ischemia was found to fall equally or more often in response to personally relevant mental stress as compared to exercise; this mental-stress induced ischemia was usually asymptomatic. Patients with CAD who showed LV wall motion abnormalities during laboratory mental stress testing had a significantly increased likelihood of exhibiting myocardial ischemia during daily activities as assessed using ambulatory monitoring. Laboratory mental stress-induced myocardial ischemia also is associated with a longer duration and increased frequency of ischemia during daily activity.
Mental stress–induced myocardial ischemia invariably occurs at a lower double product than that evoked by exercise, while diastolic pressor responses to mental stress are larger.\textsuperscript{157,191,196,231} Controlling for the change in double product, beta-endorphin secretion is greater in mental stress compared to exercise, which may explain the predominance of silent, as opposed to symptomatic, myocardial ischemia induced by mental stress.\textsuperscript{252,239} It has been suggested that not only increased oxygen demand, but also decreased O\textsubscript{2} supply may contribute to myocardial ischemia during mental stress.\textsuperscript{9}

**Mechanisms of Decreased Myocardial O\textsubscript{2} Supply**

**CORONARY ARTERY SPASM**

A major determinant of oxygen supply to the myocardium is the caliber of the coronary vessels. The luminal caliber of the coronary arteries can be compromised not only by stress-mediated processes and other environmental factors leading to atherosclerosis, but also by coronary arterial vasospasm. Coronary artery spasm is a dynamic mechanism that compromises blood flow in variant angina pectoris, as well as in ischemic heart disease in general.\textsuperscript{405} Furthermore, vasospasm of epicardial coronary arteries can occur in response to increased adrenergic and vagal activity, thromboxane A\textsubscript{2}, and endothelin-1.\textsuperscript{393} A number of substances that rise with the stress response, e.g., adrenergic neurotransmitters, angiotensin, and insulin, exert a trophic influence on vascular smooth muscle. These vessels with hypertrophied smooth muscle show an increased responsivity to vasoconstrictor substances.\textsuperscript{97,181,172} In addition, endothelial damage, which can be mediated by stress-induced turbulent blood flow,\textsuperscript{275} can render arteries vasoconstrictive, even in response to normally vasodilating substances such as acetylcholine.\textsuperscript{115,183,276} Angiographic studies among patients with CAD reveal that mental stress can evoke vasoconstriction in atherosclerotic coronary vessels, especially at points of stenosis.\textsuperscript{33,407} Experimental animal data links exposure to stressors such as social disruption to a paradoxical propensity for coronary arterial vasoconstriction in response to intracoronary acetylcholine.\textsuperscript{396}

Stress mechanisms also are implicated among patients with Prinzmetal angina, for whom changes in autonomic outflow (withdrawal of vagal tone as indicated by diminished high frequency component of heart rate variability) were found to consistently precede episodes of ST segment elevation. This finding was irrespective of the presence or absence of coronary artery stenoses.\textsuperscript{203}

Clinicians have long recognized that the vasospastic component of angina pectoris tends to be expressed more in the winter months. Exposure to extreme cold is unpleasant and evokes vasoconstriction by direct action upon the blood vessels and by a reflex increase in sympathetic activity. In coronary patients, as well as in normal subjects, the cold pressor test (immersion of the hand in cold water for 1–3 minutes) induces significant increases in systolic and diastolic blood pressure and marked elevations in norepinephrine and epinephrine levels.\textsuperscript{14,20,27,146,262,304} Angiographic studies reveal that the cold pressor test can provoke coronary vasospasm in patients with Prinzmetal angina or with coronary atherosclerosis.\textsuperscript{154,177,269,299,406} Female factory workers showed a significantly increased risk of ST segment depression during work in inverse relation to occupational temperature levels (OR 0.77, CI 0.62–0.95), after adjusting for age, type of work, smoking, and relative weight.\textsuperscript{226}

Rebound coronary artery vasospasm also can result from withdrawal from exposure to nitrates among workers in the explosives industry. Nitroglycerin appears to reverse this effect.\textsuperscript{306,391}
CARBON MONOXIDE EXPOSURE

Exposure to carbon monoxide (CO) impairs oxygen supply to the myocardium due to the high binding affinity of CO to hemoglobin and a leftward shift in the \( O_2 \) dissociation curve.\(^{128} \) Among patients with CAD, exposure to low levels of CO (carboxyhemoglobin levels of 1.5–4%) is associated with a diminished exercise time to onset of ischemic ST changes and to angina pectoris.\(^{1,189,305} \) (By way of reference, carboxyhemoglobin levels found in smokers range from 2–15%,\(^{151} \))

REDUCTION IN CORONARY BLOOD FLOW VELOCITY

Another mechanism by which mental stress may act to compromise oxygen delivery to the myocardium is by diminishing coronary blood flow velocity. Acute mental stress can increase blood viscosity and decrease circulating plasma volume.\(^{105} \) Among patients with syndrome X, performing mental arithmetic gave rise to a significant fall in coronary blood flow together with a significant increase in arterial norepinephrine; 13 of these 29 patients developed typical angina-like chest pain. There were, however, no significant changes in the diameter of the left anterior descending coronary artery during this mental stress.\(^{51} \) Increased coronary microvascular resistance has been proposed as the mediating mechanism of myocardial ischemia in Syndrome X.\(^{51,175} \)

LEFT VENTRICULAR HYPERTROPHY

LVH, which is closely related to workplace BP, can compromise myocardial oxygen supply. This is due to high end-diastolic pressure which compresses the intramyocardial vessels, as well as to a low capillary density of the large myocardial mass, with a lowered coronary flow reserve.\(^{75,118,271,284} \)

Mechanisms of Increased Myocardial \( O_2 \) Demand

LEFT VENTRICULAR HYPERTROPHY AND ESSENTIAL HYPERTENSION

LVH also is associated with an augmented myocardial oxygen demand, due to increased pressure load and the burden of a large myocardial mass.\(^{75} \) Myocardial oxygen demand is chronically increased in essential hypertension with or without LVH; this is related to elevated total peripheral resistance, which places an increased afterload on the heart. Based on these considerations, it is not surprising that patients with essential hypertension often have angina pectoris even in the absence of CAD.\(^{188} \)

ELEVATED BLOOD PRESSURE AND/OR HEART RATE

Superimposed acute stressors create an inotropic and chronotropic demand for yet more oxygen to the myocardium. In patients free of manifest CAD but with stable essential hypertension with or without LVH, transient episodes of myocardial ischemia are found to be related to peaks in ambulatory BP\(^{12,266} \) In some\(^{266,293} \) but not all\(^{12} \) reports, these episodes were significantly more frequent in hypertensive patients with LVH. Deedwania and colleagues found, by simultaneously recording ambulatory BP and ECG, that most episodes of silent myocardial ischemia in patients with CAD are preceded by an elevated systolic BP, as well as heart rate.\(^{68,69} \)

Isometric stress elicits a powerful diastolic pressor response. In CAD patients, this response can lead to myocardial ischemia, which is attributed to augmented oxygen demand from LV afterload. Isometric maneuvers such as handgrip are less consistent triggers of myocardial ischemia than dynamic exercise; the latter leads to a greater increase in double product.\(^{46,144,178} \) Upper extremity activity may entail a greater isometric component than lower extremity activity.\(^{155} \)
Acute heat exposure, particularly with physical exertion, gives rise to a tachycardic response.\textsuperscript{71,336} There are some reports of ST depression associated with heat-elicited tachycardia among workers in a precision casting factory,\textsuperscript{558} as well as among normal subjects and CAD patients exposed to the intense heat of a sauna.\textsuperscript{563} Other studies in milder conditions ($\leq 30^\circ \text{C}$) failed to elicit any signs of myocardial ischemia in CAD patients.\textsuperscript{2,336}

Elevations in the double product and in diastolic BP have been reported in response to short-term exposure to noise levels in the range of 85–95 dB,\textsuperscript{6,385} although there are conflicting reports concerning chronic noise exposure and BP effects.\textsuperscript{147,197,241,361} There is suggestion of a possible association between occupational noise exposure and risk of myocardial ischemia: noise-exposed male factory workers showed a borderline significant increase in odds ratio for ST depression during work (OR 1.07 CI 0.99–1.12), after adjusting for age, type of work, smoking, and relative weight.\textsuperscript{126}

**Empirical Data**

Reported mental stress during general daily activities has been found to be associated with ischemic electrocardiographic changes in patients with coronary heart disease.\textsuperscript{19,110,117} Gabbay and colleagues found that among 63 patients with CAD, "mental activities (appeared) to be as potent as physical activities in triggering daily life ischemia."\textsuperscript{117} None of these studies, however, specifically examined stressful work activities.

There has been considerable attention paid to the circadian pattern of myocardial ischemia. Transient electrocardiographic signs of myocardial ischemia show a nadir during sleep and a peak in the morning hours after waking. This peak corresponds to the time of maximum heart rate and systolic BP, as well as high levels of catecholamine and cortisol which increase the sensitivity of coronary arteries to catecholamine-mediated vasoconstriction.\textsuperscript{21,123,375,400} The relation of this circadian distribution of myocardial ischemia to shiftwork and other occupational factors remains to be determined.

Driving is known to be a highly stressful activity, and professional drivers are at inordinately high risk of developing ischemic heart disease (IHD).\textsuperscript{22,380,401} While there are no published Holter monitoring studies among professional drivers with cardiovascular disease, recordings during driving have been reported among amateur drivers with IHD. In one study, a 20-minute drive in heavy London traffic elicited STT changes in 13 of 24 stable IHD patients.\textsuperscript{362} Another also reported ischemic electrocardiographic changes among a series of IHD patients during driving.\textsuperscript{204} A third study, however, did not find any driving-related ST changes in five patients with angina pectoris, but two of the five developed chest pain while driving.\textsuperscript{219} More recent data reveals that among 22 IHD patients, driving into a speed trap was associated with a significant chronotropic effect, with some cases of silent, as well as symptomatic myocardial ischemia.\textsuperscript{58}

There are a few reports of ambulatory monitoring during work made among subjects without apparent IHD. Green and colleagues made 1-hour Holter recordings during work among 2508 factory workers without a history of IHD to examine the relation between ST-segment depression and exposure to the physical factors of noise and cold.\textsuperscript{126} Asthall and colleagues reported that among male police officers 45 years or older with 2+ cardiac risk factors but without known IHD, there was a 3.4% prevalence of ST-segment depression during 24-hour ambulatory monitoring, which included shiftwork; followup thallium perfusion scans were negative.\textsuperscript{11} Of 18 precision casting factory workers examined by Taccola, et al., five exhibited tachycardia and STT changes during physical exertion and radiant heat exposure.\textsuperscript{358} Asmar and
colleagues found self-rated work stress levels were significantly higher among asymptomatic hypertensive patients who had ST-segment depression during ambulatory monitoring, compared to those without signs of myocardial ischemia. There is a general paucity of systematic study on myocardial ischemia in relation to work activity. In particular, comprehensive and integrative examination of the psychosocial, ergonomic, and physical-chemical work environment, as it affects the occurrence of myocardial ischemia, is lacking. Especially surprising is the lack of published data on this topic among series of patients who have returned to work after acute cardiac events. Kavanagh and Matosevic have provided descriptive reports on several post-myocardial infarction patients in whom laboratory exercise testing was normal, but who developed significant ST-segment depression during specific physically and mentally stressful work activities. These authors consider that the work-site ambulatory data was essential for making recommendations concerning their patients' occupational activity.

Krantz and colleagues have stated: "Research on [myocardial] ischemia has provided a pathophysiologic model for understanding mechanisms by which mental stress may trigger clinical events." Clearly, such a model needs to be focused on the work environment.

**ATHEROGENESIS, COAGULATION, AND STRESS MECHANISMS** by Andrew Steptoe, DPhil, and Michael Marmot, PhD

Atherogenesis is the process through which atherosclerosis is initiated and develops over the lifespan. Understanding of the early stages of atherogenesis has increased substantially over the past decade, with the recognition of the central importance of inflammatory responses and injury to the endothelial surface of the arterial vessel wall. Endothelial damage, particularly at branching points of the arterial tree, results in plaque formation, involving the trapping of lipoprotein and adhesion of monocytes and T lymphocytes. Continued cell influx and proliferation leads to more advanced lesions and fibrous plaque formation. Pro-inflammatory cytokines (soluble proteins that regulate cellular behavior) such as interleukin 1, interleukin 6, and tumor necrosis factor-α are critically involved in atherogenesis. They impair endothelial function and stimulate macrophage accumulation and migration of smooth muscle cells into lesions. These cytokines also are associated with insulin resistance and the cardiovascular metabolic syndrome (see page 146).

Endothelial damage is most likely to occur at branching points on the arterial tree where there is turbulent blood flow. Hypertension has a major influence on shear stress at these sites, and also has direct pro-inflammatory effects, such as increasing the formation of free radicals. Therefore, the influence of work stress on atherogenesis may be mediated in part by hypertension. Angiotensin II, an important component of the renin-angiotensin system, also may increase during stress, contributing to atherosclerosis by stimulating vascular smooth muscle cell growth.

Direct evidence for the effects of stress on endothelial dysfunction is available in animal studies, since social stress in cynomolgus monkeys causes endothelial injury in atherosclerotic arteries. This response is inhibited by beta-adrenergic blockade, implicating sympathetic nervous system (SNS) activation. Behavioral stress also has been shown in animal studies to stimulate the production of pro-inflammatory cytokines. The function of the endothelium is dependent on nitric oxide (NO), which inhibits adhesion of platelets and white cells to vessel walls, and
on the growth of vascular smooth muscle cells. NO has been found to be involved in the vasodilatory response to mental stress. Hypertensive patients show blunted forearm vasodilation to mental stress, and this effect is mediated by impaired NO production. Although no studies linking NO and cytokines with work stress have been described yet, these factors are potentially of great importance.

The role of inflammation in atherogenesis also has raised the possibility that infections contribute to coronary heart disease (CHD). Markers of systemic inflammation such as plasma C-reactive protein concentration are associated with future myocardial infarction and stroke. Associations between CHD risk and persistent infection with *Helicobacter pylori*, *Chlamydia pneumoniae*, and cytomegalovirus have been suggested.

The extent of lipoprotein incorporation into plaque depends on the concentration of lipids in the blood. Atherogenesis is positively associated with the concentration of total cholesterol and low-density lipoprotein (LDL) cholesterol, and negatively correlated with high-density (HDL) cholesterol. LDL cholesterol accumulates in vessel walls, where it becomes oxidized, stimulating other processes such as damage to the endothelium and the formation of foam cells. Behavioral stress stimulates increases in the concentration of cholesterol in some animal models. Stress also stimulates total cholesterol and LDL cholesterol acutely in humans, although this response is due in part to changes in hemoconcentration, since plasma volume often decreases during stress, leading to increases in concentration without increased synthesis. Long-term, episodic, naturalistic stressors—such as important academic examinations—have been found to alter lipid concentration in some studies, but not others. However, it has proved difficult to demonstrate the effects of variations in work demands on lipid levels within subjects. Any such changes that take place might be due to alterations in dietary fat intake, since this also increases with workload in some individuals.

Cross-sectional associations between lipids and job characteristics such as work demands and job control also have been inconsistent. In the Whitehall II study of British civil servants, total cholesterol was not related to occupational grade, and differences in CHD risk associated with factors such as low job control were independent of cholesterol. There were occupational grade differences in apolipoproteins A-I and B, but these were explained quite substantially by concomitant variations in health-related behaviors such as smoking, exercise, and diet. However, associations between high effort and low reward and elevated total and LDL cholesterol that are independent of lifestyle factors have been described in studies from Germany and Sweden. Note that the well-established association between carbon disulphide and CHD may be mediated by the influence of this chemical on LDL cholesterol and blood pressure.

The later stages of CAD and the development of acute ischemic syndromes are dominated by the process of thrombogenesis. As the disease progresses, arterial plaques characterized by thin, fibrous caps, substantial lipid accumulation, and a large number of macrophages are particularly vulnerable to disruption. The disruption of unstable plaques is an important process in acute thrombosis, and complications are influenced by a number of factors such as catecholamine release and the concentration of fibrinogen. These substances, in turn, affect platelet activation and other coagulation processes.

Fibrinogen plays an important role in the coagulation cascade, since it is converted to fibrin (a major constituent of thrombi) by thrombin. In conjunction with other hemostatic factors, fibrinogen promotes atherosclerosis by stimulating platelet
aggregation and increasing blood viscosity, foam cell formation, and smooth muscle proliferation. It also may be important as an acute phase protein associated with inflammatory processes. Sjogren has suggested that occupational exposure to inhaled dust microparticles may provoke alveolar inflammation and the release of mediators such as fibrinogen. Fibrinogen has been found prospectively to predict incidence of CHD. Early studies relating work stress with fibrinogen concentration produced inconsistent findings. The issue therefore was investigated more comprehensively in the Whitehall II study. It was found that higher fibrinogen concentrations were associated with lower socioeconomic status in both men and women. Control over work, as assessed independently by managers, was inversely associated with fibrinogen concentration in both sexes. Fibrinogen also is associated with high effort and low reward at work. Thus, it may be an important marker of the pathways through which work and other psychosocial factors influence CHD risk. Other hemostatic factors that are associated with work stress include tissue plasminogen activator (tPA), which regulates fibrinolysis. A study of Japanese middle-aged workers demonstrated that tPA was inversely associated with psychological job demands independently of standard risk factors.

Currently, there is considerable interest in clinical research on the role of platelets in acute cardiac syndromes, with platelet activation and platelet size both as important parameters. Platelets adhere to damaged endothelium, and their granules contain cytokines that stimulate the proliferation of monocytes and smooth muscle cells. Activated platelets also recruit further platelets into thrombi. No studies have been reported to date that relate platelet function with work characteristics. However, platelet activation as assessed by platelet factor 4 and beta-thromboglobulin is increased by acute emotional stress. These acute responses probably are stimulated by catecholamine release. Cross-sectionally, associations between platelet activation and other psychosocial factors have been described. For example, Markovitz found that platelet activation in CHD patients was positively correlated with hostility scores, and platelet responsivity is heightened among patients with clinical depression. Both hostility and depression are factors that have been linked with increased CHD risk. It is possible, therefore, that the stimulation of thrombogenesis through enhanced platelet activation is another process that mediates psychosocial influence on cardiac events.

Current understanding of atherogenesis and thrombotic mechanisms highlights a number of pathways that are sensitive to stress-related neuroendocrine responses. Research linking these factors with the work environment is lacking. However, it is likely that much of the effort in gaining understanding of how the work environment affects CHD will be focused on these pathways over the next few years. This endeavor will be facilitated by the establishment of proxy measures of CHD, of which two of the most promising are carotid intima-media wall thickness and plaque height. These measures can be taken noninvasively with high resolution carotid ultrasonography. Thickness of the carotid intima-mediated wall and height of carotid plaque are associated with CV risk factors and increased risk of CV events. Progression in the development of carotid atherosclerosis over 4 years has been shown in Finnish men to be more rapid in those experiencing high demands and low economic rewards at work than in others with low demands and high rewards. The integration of this index into population studies of other factors influencing atherogenesis will allow greater precision in prediction and understanding of mechanisms.
Evidence for Mediating Econeurocardiologic Mechanisms

NEUROENDOCRINE MECHANISMS by Töres Theorell, MD, PhD

Increasing awareness of the fact that most processes in the body are integrated in complicated CNS-end-organ interactions has had a profound impact on today's cardiology. The endocrine system could be regarded as an organ that is played upon by the brain. Overuse of it may cause many disturbances. "Chords" produced by the brain may be "harmonic" or "disharmonic." The effect of a short disharmonic chord may not be deleterious to the listeners (in our analogy: the body), but a long-lasting disharmonic one can disturb the whole audience.

Selye's hypothesis about the general adaptation syndrome (GAS) describes three different stages in the reaction to a situation that requires unusual energy mobilization:132

1. Alarm—an immediate reaction that the cortex of the brain is not aware of initially. Alarm causes arousal of some of the fast-reacting endocrine systems that are central in the mobilization of energy, such as the catecholamines adrenaline and noradrenaline.

2. Defense—a slightly slower reaction (within minutes) that is paralleled by cognitive processes. The cognitive functions include thoughts about how to handle the situation, immediate expectations, etc. The hormonal reactions in this phase aim at facilitating all aspects of the situation in which energy mobilization takes place. Release of fuel to the blood is the central aspect; lipids and glucose serve as fuel and are necessary in the energy production needed for muscular action (running or fighting). Several hormonal reactions ready the body to fight for a long time: the body becomes insensitive to pain, coagulation is facilitated (for the avoidance of excessive bleeding when injury occurs), retention of fluid and salt is facilitated (for the avoidance of excessive loss of plasma volume if sweating continues and there is no possibility to drink or to ingest salt), and some aspects of the immune system are activated. All of these components of the defense reaction are mirrored by physiological and endocrine processes that can be monitored in human beings.

According to Folkow, the defense reaction has "the greatest relevance for the cardiovascular system." In its classical manifestation, it is an integrated cognitive-hemodynamic-metabolic response preparing the organism to physically cope with threat or challenge. Components of the defense response include sympathetic, adrenergically-mediated increased cardiac output with blood flow directed to the vasodilated skeletal muscles, heart, and brain; higher CNS suppression of baroreceptor vagal activity, yielding simultaneously increased heart rate; efferent renal SNS activation leading to decreased renal blood flow with lowered glomerular filtration rate, increased sodium retention, and increased blood volume, and activation of the renin-angiotensin system and antidiuretic hormone secretion; insulin resistance, to insure adequate glucose to the brain; and platelet activation, in anticipation of injuries.3,8,97,166 Obviously, the defense reaction may lead to adaptation (phase 2 of Selye's GAS), which represents a successful reaction to the environment, and the energy mobilization calms down. But the same reaction also may be unsuccessful and result in defeat or loss of control, which could be regarded as an alternative stage:

3. Exhaustion—either the end stage of an unsuccessful GAS, or the defeat phase of Henry's theory.142 During this phase the limitations of the organism are shown and there is a breakdown of adaptation. There are several new concepts that partly overlap this one, such as burnout and vital exhaustion (psychologically defined) and chronic fatigue syndrome (physiologically defined).
A long-lasting physiological adaptation is associated with disturbances of the hypothalamic-hypophyseal-adrenocortical axis. The defense and defeat reactions may alternate and coexist in real life, and in vulnerable hearts this may have cardioleterious effects (see Chapter 4).

The GAS according to Selye is an example of response stereotypy. One of the strongest critics of Selye's theory has been John Mason, whose main point was that there is no such general phenomenon as the GAS. Every individual and every situation is unique. Mason's idea could be regarded as an argument for response specificity, in which every individual/situation combination induces a unique set of endocrine reactions. Of course, both stereotyped and specific responses occur.

One of Mason's central concepts was anabolism, which corresponds to endocrine processes stimulating growth, restoration, and replacement of worn-out tissues. Unfortunately, anabolism, which is necessary for long-term survival, is inhibited by long-lasting energy mobilization. In line with Mason's reasoning, energy mobilization (in its extreme form, catabolism) and anabolism could be regarded as the two most essential concepts in the organization of our knowledge of endocrine processes of relevance to the interplay between psychosocial work environment and CVD.

Acute Energy Mobilization

There is a profound difference between acute and long-lasting mobilization of energy. The acute process has been studied extensively in experiments. It is characterized by initial release of the catecholamines adrenaline and noradrenaline (NA) to the blood, followed within minutes by release of glucocorticosteroids and mineralocorticosteroids. This is a necessary sequence of events if the organism is to survive in a critical situation, and absence or attenuation of it is accordingly evidence of a disturbance.

Catecholamines

Assessment Issues. In preventive and clinical cardiology, it is possible to measure the catecholamines in urine and blood. The reader should be aware of the difficulties in this area.

- Plasma catecholamine determinations: When measuring catecholamines in blood, remember that the fluctuations are so rapid that casual measurements may be meaningless. Furthermore, venipuncture induces pain, which immediately results in elevated catecholamine levels. Such an elevation is, of course, induced by a situation that is irrelevant to the relationship between the psychosocial work environment and CVD. One possibility is to measure the blood catecholamines by means of a venous catheter, which allows repeated blood sampling without repeated venipunctures. It is difficult, however, to make repeated samplings during work activities. To obtain a representative measurement of catecholamines during basal conditions, the physician may make the sampling after a resting period post insertion of a venous catheter.

The plasma NA concentration is to a large extent a reflection of muscular activity, which results in NA influx into the blood. Furthermore, NA reflects the activity in the SNS, which could react very differently in different parts of the body (e.g., specific reaction patterns in the gastrointestinal system, heart, and/or lungs). Therefore, plasma adrenaline (which is a weaker but “cleaner” indicator of mental stress than NA) frequently correlates more strongly with BP during restful conditions than does plasma NA. Hjemdahl formulates this in the following way:
Plasma NA is a frequently used marker for sympathetic nerve activity in humans, but the data obtained are often misinterpreted due to lack of appreciation of the physiological determinants of the NA concentration measured. NA overflow from an organ gives a good reflection of nerve activity in that organ. However, sympathetic nerve activity is highly differentiated, particularly during stress, and conventional plasma NA levels (usually forearm venous samples) cannot be taken as an indication of "sympathetic tone" in the whole individual. NA is rapidly removed from the plasma, resulting in meaningless net veno-arterial concentration differences over organs unless its removal from arterial plasma is taken into account. In the forearm, for example, 40–50% of catecholamines are removed during one passage; about half of the NA in a venous sample is derived from the arm and half from the rest of the body. Therefore, conventional venous sampling overemphasizes local (mainly skeletal muscle) nerve activity.149

With regard to adrenaline the physiologic background is different. Goldstein has formulated this in the following way:

Since the adrenal medulla secretes [epinephrine] EPI directly into the bloodstream, plasma EPI levels generally reflect neural outflow to the adrenal medulla. Thus, increments in adrenomedullary secretion of catecholamines resulting from manipulations of circulatory reflexes or from ... administration of drugs correlate with increments in directly recorded adrenal nerve activity ... however ... plasma levels of adrenaline are very low in antecubital venous plasma of healthy volunteers at rest—as little as 3 x 10⁻¹¹ mol/L. This contrasts with plasma levels of NE, which normally exceed 6 x 10⁻¹⁰ mol/L.153

Urinary catecholamine determinations: A useful approach is to measure catecholamines in urine. Urinary sampling of catecholamines is more suitable than plasma determinations for field studies. Hjemdahl has noted that urinary NE reflects arterial NE levels, and that changes in urinary EPI appear to reflect its secretion during stress, as well.149

The relevant measures are the amounts of excreted adrenaline and NA into the urine per time unit. To obtain such measurements, it is necessary to record the exact hours of urination and to collect all the urine during a given period. This can be a difficult doctor-patient collaborative task, and it requires good preparation. The excretion of adrenaline and NA fluctuates during the 24-hour cycle. For adrenaline, the excretion during the most active part of the day is three times higher than that during deep sleep at night. Accordingly it is important to define the period of collection during the day. The shorter the period of collection, the more difficult it is for the patient to successfully collect during the defined period, although he or she could be instructed to drink water to increase urination.

The strength of the urinary measurement of catecholamines is that it reflects excretion over a defined period of time; it provides the physician with an integrated assessment of catecholamine excretion during several hours, for instance during an ordinary 8-hour working day. Early in the development of these assessments, it was proposed that work-free days should be compared with working days to minimize the effect of interindividual variation in basal excretion of catecholamines.20 The assessment provides information about the intrindividual increase in catecholamines during working hours. Because of the marked diurnal variation in catecholamine output, corresponding hours during the work-free day and the working day should be compared.

Evidence for Mediating Echocardiographic Mechanisms
There are several technical errors that may occur in the measurement of catecholamine excretion in the urine. Ingestion of certain kinds of food or fluids, for instance bananas and coffee, could influence the assessments. The urine must be acidified to withstand the breakdown of catecholamines. Usually hydrochloric acid is added in the aliquot before collection starts. If there is uncertainty regarding the completeness or timing of the collection, the excretion could be related to the amount of creatinine that is excreted. In summary, assessment of catecholamine excretion must be prepared carefully and in consultation with experts.

**Empirical Findings On Work Stressors and Catecholamine Excretion.** The classical work of Levi and Frankenhaeuser illustrated the usefulness of the assessment of urinary catecholamine excretion as an indicator of arousal in the workplace. In additional studies, Fröberg, et al. showed that sleep deprivation caused marked elevation of urinary adrenaline and NA urinary excretion, an observation that has relevance to the growing scientific evidence that exposure to shiftwork increases the risk of developing MI. Johansson, et al. and Lundberg and Frankenhaeuser showed that monotonous, high-pressure work induces elevated catecholamine excretion. Rissler and Elgerot showed that a long-lasting period of overtime work causes not only elevated excretion of adrenaline and NA but also a delayed relaxation of the arousal function in the evening. The overtime study indicated that it may take weeks before such a disturbance disappears after the end of the overtime work.

Other experiments demonstrated that piece-rate work under high pressure induced marked elevation of urinary catecholamine excretion. Field studies revealed that Swedish city bus drivers had approximately twice the average level of adrenaline excretion compared to other occupational groups. Urinary catecholamine excretion was shown to be rising as a function of traffic congestion among male Los Angeles metropolitan bus drivers. Frankenhaeuser, et al. found that a group of working women had elevated catecholamine excretion after work when they were confronted with the home situation.

A study of male prison employees showed that the urinary excretion of adrenaline and NA was related to decision latitude: employees with a low degree of decision latitude had high catecholamine output, even after adjustment for body mass index, coffee and alcohol drinking, and age. The above-mentioned study of urinary excretion of adrenaline in bus drivers showed that drivers who reported job strain (high psychological demands and low decision latitude) had a higher urinary catecholamine output than others.

**Cortisol**

**Metabolic (Catabolic) Effects of Cortisol on CVD.** The hypothalamic-pituitary-adrenocortical axis (HPA) originates in the hypothalamus, which responds to arousal situations by increasing the output of corticotrophic releasing factor (CRF). CRF stimulates the pituitary to increase the output of adrenocorticotropic hormone (ACTH). ACTH, in turn, stimulates the adrenocortex to increase the output of those corticosteroids that have an important role in the energy mobilizing process. The HPA axis has to function well in terms of excitability—cortisol should increase in situations that require energy mobilization—but it also must slow down once the situation has calmed. Cortisol inhibits the preceding steps in the chain—the release of ACTH and CRF.

Cortisol has been the most extensively studied of the corticosteroids with predominantly energy mobilizing function. It has both mineralocorticoid and glucocorticoid
effects, and it reacts less rapidly (within minutes) than catecholamines to a challenge. Accordingly, it is meaningful to study serum cortisol variations in real-life situations.

Cortisol is a counter-regulatory hormone that protects against insulin-induced hypoglycemia. Many of its effects facilitate the effects of other hormones that are important in energy mobilization and arousal. For instance, it enhances and prolongs the effects of epinephrine and glucagon, promotes hepatic gluconeogenesis and glycogen synthesis (glycogen then is acutely released in response to adrenaline and glucagon), and inhibits peripheral glucose utilization. Physiologically, cortisol enhances the vascular reactivity to angiotensin II and NA. It also promotes dyslipidemia by increasing very-low-density lipoprotein (VLDL) secretion and then enhances the transformation of VLDL to low-density lipoprotein. It has been documented that cortisol stimulates vigilance and CNS arousal.

**Cortisol Assessment.** The plasma concentration of cortisol is not as rapidly fluctuating as that of catecholamines; thus, it is more meaningful to measure cortisol in plasma. The venipuncture itself causes an elevation of serum cortisol, but it takes several minutes, and therefore the use of a venous catheter is not necessary. Under normal conditions, a rising plasma cortisol level indicates a rising level of arousal. There is a marked circadian pattern, with high levels in the morning hours and gradually falling concentration during the mid-day and afternoon hours. Therefore, it is important to take hour of sampling into account when assessments are interpreted. Under most conditions it is favorable to measure the concentration in the morning. As with catecholamines, potential confounders include medication, smoking, alcohol, and food. Mostly free (not bound to protein) cortisol is measured.

Free cortisol also can be measured in urine (see precautions regarding urine collection of catecholamines, pages 141–142). Another method is saliva analysis. The saliva concentration of cortisol has been shown to reflect the free cortisol concentration in serum, and since repeated saliva samples can be collected more easily than repeated blood samples, the physician can study circadian variations of cortisol during real-life conditions. The patient can carry capillary tubes, which are inserted into the mouth for saliva collection many times during the day.

- **Empirical findings concerning work stressors and cortisol.** The interpretation of the relationships between work stressors and cortisol excretion has been complicated by the fact that acute and long-term effects of stressors have been mixed. However, in normal healthy samples, short periods of stressful work do induce measurable elevations in plasma cortisol as well as urinary and salivary cortisol. For instance, studies of bus drivers have shown increasing cortisol excretion in relation to traffic peaks. In a large study of prison employees, Härenstam and Theorell showed that employees in work sites with many psychosocial problems had higher plasma cortisol than other employees.

- **Empirical neuroendocrine findings in effort-distress or low control–high demand situations.** The Effort-Distress Model (EDM) is based on performance of a monotonous task that requires much effort and vigilance, leading to arousal and substantial distress. This combination has been found to activate both the sympathoadrenalomedullary and pituitary adrenocortical axes, while an enjoyable, self-paced task yields only a rise in urinary epinephrine. Corroborative data from the worksite is provided by Timio and Gentili, who reported significantly elevated epinephrine, norepinephrine, and 11-hydroxycorticosteroid excretions among healthy metallurgists when performing paced assembly work with no control over
work pace, compared to "ordinary work" outside the assembly line. Experimental data on social interactions and conflicts in mice are quite coherent with these workplace and human laboratory observations. Henry and Stephens found that elicitation of the defense (fighting to achieve a dominant position) and the defeat (submission) responses activated the sympathoadrenal and the pituitary adrenocortical systems, respectively.142

The EDM's distress and eustress reactions parallel the high demand-low control "job strain" situation (corresponding to distress) and high demand-high control "active job" situation (corresponding to eustress) when the Demand-Control Model is used as a framework. Of course, an important distinction is that the demand-control model focuses on the workplace environmental demands and constraints, whereas the EDM focuses on the individual's reaction to the laboratory environment.

Long-Lasting Energy Mobilization
Sustained exposure to situations that are uncontrollable, unrewarding, and demanding could induce repeated elevations of catecholamines and energy-mobilizing corticosteroids. Such iterative endocrine reactions by themselves may have profound effects on the CV system. The measurement of these endocrine reactions during long-lasting energy mobilization, however, is another matter. Scientific confusion existed in the literature before it was realized that the regulation of arousal can be disturbed if exposure to a psychosocial stressor is long-lasting. Some endocrine systems may be "set" on a higher activity level due to such exposure; for instance, the thyroid hormones may be elevated after long-lasting exposure to arousal in sensitive persons. However, cortisol regulation also may change.

Recently, Sluiter, et al. showed that long-distance truck driving with extremely long work hours causes a low excretion of adrenaline and noradrenaline as well as an abnormal cortisol circadian rhythm.340 In the usual cortisol pattern, levels are high in the morning and start declining at 10 AM. Low levels are found before bedtime. In the long-distance truck drivers, the day after driving was characterized by low morning cortisol levels, which peaked after a couple of hours. This is an example of an early disturbance of the regulatory system. After even longer periods of arousing situations, however, more profound disturbances can arise. These more profound regulatory cortisol disturbances can take several forms, and they all have relevance to heart disease:

1. **Constantly elevated cortisol**, as in clinical depression. The normal inhibition of the drive in the HPA axis is not functioning.317 Using symbolic language, this could be labeled "brake failure." Depression is an important risk factor with prognostic and therapeutic implications, particularly in rehabilitation after MI.

2. **Exhausted function**, as in the chronic fatigue syndrome (CFS). Cortisol levels are low, with very small variations, as though the HPA axis has stopped responding.72 This could be labeled "accelerator failure," and it has relevance to the two psychologically defined concepts *vital exhaustion* and *burnout*. Vital exhaustion has been studied extensively in relation to heart disease risk.192

3. **Elevated sensitivity**, as in the post-traumatic stress disorder. If a subject has been exposed to extreme stress, such as torture and rape, serum cortisol concentration becomes markedly elevated for many weeks and months. This elevation may result in increasing numbers and sensitivity of cortisol receptors, so that only small amounts of cortisol are needed to induce marked effects. With such a disturbance, the arousal function shows marked fluctuations, in particular when the subject is reminded of the traumatic events that caused the disturbance.47
The HPA axis is associated with other functions. Hypothetically, an “exhausted” HPA axis function may be compensated for by overactivity in parallel systems. For instance, patients with CFS have shown elevated plasma concentration of NA. CFS also may be associated with overactivity in parts of the immune system, such as increased responsiveness of the natural killer cells and interleukins to physiologic stressors. This overactivity may be part of the explanation why vital exhaustion is associated with a marked elevation of CV risk.

**Inhibition of Anabolism**

Michelson, et al. provide some mechanistic details to corroborate the downplaying of anabolic steroid synthesis in periods of crisis, “adaptive redirection of energy,” showing that CRF inhibits LNRH, and that glucocorticoids suppress a number of sites in the reproductive endocrine axis—LNRH, gonadotropins, testosterone, and estradiol—as well as decrease the target tissue’s response to these sex hormones.

Accordingly, energy mobilization often is associated with inhibited anabolism. This inhibition can be measured by means of changes in testosterone in men. Interestingly, recent studies show that a disturbed cortisol rhythm, with low morning levels and small variations, is associated with low testosterone levels in men. Theorell, et al. demonstrated that increasing job strain is associated with decreasing total plasma testosterone. In a recent study of a police organization, Grossi, et al. found that police officers who lost their jobs because of a reorganization had relatively low plasma testosterone levels at the time of job loss, but the levels had increased 1 year later when most of them had new jobs. Those with the most satisfactory jobs had the most pronounced increases in testosterone concentration. Serum lipids also had improved significantly, illustrating a pattern of CV risk factor improvement.

Stress-mediated elevations in plasma prolactin, as shown among nurses reporting high job strain and among subway drivers with “person-under-train” incidents, could be regarded as a manifestation of “passive coping,” which also could suppress the reproductive endocrine axis via inhibition of LNRH.

Rosmond and Bjornorp have proposed that repeated arousal causing marked, iterative serum cortisol elevation is part of the etiology of the metabolic syndrome (which may include abdominal obesity, atherogenic lipid patterns, diabetes, and hypertension). Part of the reason why long-term exposure to cortisol elevation is associated with decreased testosterone production and with the metabolic syndrome may be that the synthesis of energy-mobilizing steroids is favored over the synthesis of anabolic steroids. All the steroid hormones have the same sources. The downplaying of anabolic steroid synthesis may have phylogenetic reasons. In a period of crisis, reproduction has low priority.

**Other Hormones**

Many hormones participate in the communication between brain and body. Due to space limitations, it is not possible to fully cover the effects of all of them. These processes and their interactions can be understood by understanding what a physiological reaction is. In this pursuit, the two dimensions that have been described, energy mobilization and anabolism, are helpful. Several other hormones are of relevance to the CV system.

Prolactin is a peptide that is released from the adenohypophysis. It is regulated by the dopamine and serotonin systems in the brain, both of which are important in
mood regulation. Prolactin is important to the immune system (which is stimulated) and, at least in women, to BP regulation (high levels are associated with high BP). The plasma prolactin concentration increases in situations that induce passiveness and powerlessness in crisis situations, but decreases in situations that induce free-floating anxiety. Increasing job strain in combination with depressed mood may induce marked plasma prolactin elevation in normal working men. Marked elevations also have been observed in situations characterized by sudden, unexpected loss of control, such as when subway drivers are exposed to "person under train" accident situations and when police officers lose their jobs due to reorganization.

THE CARDIOVASCULAR METABOLIC SYNDROME
by Eigil Fossum, MD, Auda Høieggen, MD, Andreas Moan, MD, PhD, Morten Rostrup, MD, PhD, Sverre E. Kjeldsen, MD, PhD

The association between blood pressure (BP) and coronary heart disease may be caused by a concurrence of atherogenic biochemical abnormalities in hypertensive patients. These abnormalities—increased total cholesterol, triglycerides, glucose, insulin, and insulin resistance—form the cardiovascular metabolic (CVM) syndrome. There are numerous reports of sympathetic nervous system (SNS) overactivity in these patients, suggesting SNS overactivity as a pathophysiological link between high BP and this syndrome.

The SNS and Hypertension
De Quattro and Chan and others identified increased SNS activity in patients with essential hypertension; increasing levels of plasma epinephrine and norepinephrine were associated with elevated BP and heart rate. Emotional stress provokes catecholamine release and has been associated with CAD. Possibly, hypertensive subjects respond to environmental stimuli with larger sympathoadrenal responses than normal subjects. Thus, elevated plasma epinephrine levels in hypertension may be a marker for an increased arousal reaction, with enhanced neurogenic activity of the type associated with the defense reaction. Such arousal is caused by awareness of hypertension, but is also a pathophysiological feature of essential hypertension.

One of the main challenges in evaluating the pathophysiological role of the SNS in hypertension is the lack of equipment capable of measuring both the rapid oscillations of the system (within seconds) and the integrated SNS response, due to advanced differentiation of the SNS branches. In the clinical setting, heart rate and plasma catecholamines are widely used. Plasma catecholamines should be measured in arterial blood because they are subject to a peripheral arterial-venous extraction of approximately 50% at rest; thus, arterial epinephrine represents the epinephrine concentration to which the tissues are exposed. In addition, plasma catecholamine concentrations in peripheral venous blood may conceal important differences between hypertensive and normotensive groups.

The concomitant increase in heart rate and BP together with reduced baroreceptor sensitivity is a characteristic feature of central nervous influence on CV adjustment and is compatible with a role of increased sympathetic tone, possibly combined with less parasympathetic inhibition of heart rate. The parasympathetic and sympathetic activities are coupled in a reciprocal, integrated response, so that an increase in the firing rate in one of these autonomic components is associated with a
decrease in activity in the other branch. The heart rate, therefore, may be an indicator of sympathetic tone. This notion is supported by studies showing significant positive correlations between plasma catecholamines and resting heart rate.

The SNS and Metabolic Disturbances

The Oslo Study of Cardiovascular Diseases showed positive correlations among BP, serum cholesterol, triglycerides, and blood glucose levels. In the Tecumseh study, those with “white coat” and sustained borderline hypertension had higher plasma triglycerides, insulin, and total cholesterol and lower values of high-density lipoprotein (HDL) cholesterol than the normotensive group. Of the hypertensive subjects, 37% had a hyperkinetic circulation with increased cardiac output and raised plasma catecholamines. Plasma norepinephrine correlated positively and significantly with cholesterol, and heart rate correlated positively and significantly with fasting insulin, suggesting activation of the SNS as a pathophysiologic link between elevation of these CV risk factors. The Tromsø Study showed that heart rate correlated significantly with the progressive increase in age-adjusted levels of serum total cholesterol, non-HDL cholesterol, and triglycerides, as well as with a decrease in HDL cholesterol in both men and women. There was a strong positive correlation between heart rate and BP, as also shown in other studies. These associations between heart rate and coronary risk factors remained significant when anthropometric and lifestyle factors were controlled.

The sympathetic activity influencing heart rate also may explain the association between heart rate and serum lipids. Several lines of evidence suggest that the SNS may influence plasma lipid levels. Public speakers and motor-racing drivers have higher heart rates, plasma catecholamines, and triglycerides when active. α-Adrenergic antagonists lower very-low-density lipoprotein (VLDL) triglyceride concentrations and increase HDL cholesterol, whereas β-adrenergic blockade gives the opposite effects.

Catecholamines have cardiovascular and metabolic hormonal effects at concentrations slightly above low-normal resting levels; even transiently and certainly chronically raised plasma catecholamine levels may cause biochemical abnormalities and deserve consideration as a pathophysiologic feature of essential hypertension. Catecholamines may increase serum cholesterol concentrations by enhancing hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and/or by decreasing receptor-mediated cellular binding and uptake of low-density lipoproteins. By stimulating α-adrenoceptors, catecholamines may decrease blood flow to peripheral vascular beds, thereby decreasing the activity of endothelial lipoprotein lipase. This enzyme is involved in the formation of HDL particles through catabolism of triglyceride-rich VLDLs.

Epinephrine has a pronounced effect on raising hematocrit, even within the lower pathophysiologic concentration range. Hematocrit is the major determinant of whole blood viscosity, which again, according to the Poiseuille-Hagen law, contributes to peripheral resistance. Accordingly, we recently showed a strong correlation between hematocrit and directly measured whole blood viscosity and insulin resistance in young normotensive men with hyper-reactive BP responses to mental stress.

In recent years, hypercoagulability and reduced fibrinolysis have been added as an integrated entity of the cardiovascular metabolic syndrome. Epinephrine activates blood platelets in vitro and increases the number of circulating platelets. Blood platelet count and function have been directly linked to cardiovascular mortality.
Increased levels of circulating epinephrine secondary to SNS overactivity may therefore explain both the metabolic disturbances and the hypercoagulability/platelet dysfunction concomitantly present in the CVM syndrome.

The SNS and Insulin Resistance

Insulin resistance has been proposed as the metabolic link between the CVM syndrome and atherosclerotic CVD.70,231 An increased sympathetic activity in hypertensive patients, directly by metabolic hormonal effects or indirectly and more chronically by inducing hemodynamic changes, may explain the association of insulin resistance and hypertension. Acutely, during low-rate infusion of epinephrine, even physiological concentrations cause intolerance to an oral glucose load and increased baseline glucose, mainly by interference with insulin action and not by inhibition of insulin secretion.131 After an infusion of epinephrine that increased the peripheral venous concentration from 25 to 75 pg/ml, both plasma glucose and insulin levels increased significantly and remained high after 2 hours.131 Inhibition of insulin secretion stems from stimulation of α-adrenergic receptors in the β cells in the pancreas,298 but seems to be of importance only at supraphysiological levels of epinephrine. Insulin resistance in the liver and skeletal muscle is mediated by β-adrenergic receptors.

The Hemodynamic Hypothesis of Insulin Resistance

Julius, et al. suggested that the relationship between BP elevation and decreased glucose extraction by skeletal muscle is secondary to hemodynamic factors; glucose delivery being a modulator of skeletal muscle glucose uptake.168 We recently found a positive correlation between forearm blood flow and insulin sensitivity103 and a negative correlation between peripheral vascular resistance and whole blood viscosity to insulin sensitivity105,150 in young normotensive men with elevated BP responses to mental stress. Pressure-induced restriction of the microcirculation may limit nutritional flow and thereby impair glucose uptake in the skeletal muscle. When epinephrine is infused intravenously, human forearm blood flow increases rather than decreases.184 Therefore, acute effects of epinephrine, though inducing insulin resistance and glucose intolerance, are insufficient to explain the hemodynamic hypothesis.

However, repeated episodes of SNS overactivity may be different from the acute effects of epinephrine infusion and may lead to structural vascular changes that further aggravate both insulin resistance and hypertension.168 High BP causes vascular hypertrophy, which is further enhanced by the trophic effects of the SNS.174 The hypertrophy increases the α-adrenergic responsiveness of the vasculature,63 which further accelerates the hypertrophy.59 The same process may lead to vascular rarefaction and insulin resistance as its functional consequence. Chronic β-adrenergic stimulation increases the size and number of fast-twitch muscle fibers, which are more insulin resistant than slow-twitch fibers. Furthermore, β-blockers aggravate whereas α-adrenergic antagonists ameliorate insulin resistance in hypertensive subjects, supporting the hemodynamic hypothesis of insulin resistance. β-Blockers decrease blood flow and increase vascular resistance, whereas vasodilators increase flow and lower resistance.

The SNS and Hyper-Reactivity to Mental Stress

Since 1986, we have studied young men selected from the military draft procedure in Oslo. As attending is compulsory, these subjects comprise all 18-year-old
men without severe medical disorders, in the Oslo area. Ten percent of these men have a screening BP ≥ 140/90 mmHg. They have normal ambulatory BP, but are hyper-reactive to mental stress. BP values recorded during the draft procedure could be considered as “office” BP, or BP during an alert reaction.

In a series of protocols, we have documented that these men with elevated screening BP and hyper-reactivity to mental stress have metabolic disturbances resembling the pattern of the CVM syndrome. The insulin-resistant men have higher BP in response to an arithmetic challenge (mental stress test) than the insulin-sensitive men. The men with the highest exercise BP responses have a significantly higher pre-exercise BP elevation (compared with ambulatory BP) than the men with the lowest exercise BP, as a mental stress response to the exercise test. Rostrup, et al. showed that the psychological stress caused by awareness of hypertension increased resting BP, heart rate, and sympathetic responses to laboratory stressors. The men selected from the higher screening BP levels, who were deliberately kept unaware of their BP status, were characterized with normal supine intra-arterial BP levels, but showed a hyper-reactive response in BP and heart rate to a mental arithmetic challenge. These data support a link between high screening BP, specific hyper-reactivity to mental stress, and catecholamine sensitive coronary risk factors.

The SNS, Workplace Stress, and the Cardiovascular Metabolic Syndrome

In our studies demonstrating a close correlation between mental stress and the components of the CVM syndrome, including BP, we used a model of acute stress. Several authors have examined the effect of chronic stress related to the workplace. Harenstam and Theorell found the urinary norepinephrine excretion to reflect self-reported work stress in a prison staff. These results were supported by Gardell, who found higher levels of catecholamine excretion, triglycerides, BP, and self-reported work stress in bus drivers working in areas with heavy traffic compared with bus drivers working in suburbs. Frohberg examined inter-shift differences
and changes during shift-weeks on different shifts with regard to urinary catecholamine excretion and self-ratings of work stress and fatigue.\(^{111}\)

The CVM syndrome, as an integrated entity, usually has not been investigated in epidemiologic studies of the workplace. However, in a prospective study of male, blue-collar workers by Siegrist, et al., the coincident occurrence of hyperlipidemia and hypertension was demonstrated empirically to have occupational psychosocial determinants.\(^{243}\) A low prospect for being promoted was a significant multivariate predictor of high-risk coronary status. This association was independent of obesity, smoking, and individual characteristics of sustained anger and competitiveness.

The link between hypertension and CAD has been strongly documented in epidemiologic studies. This association may not be casual, but may reflect a network of atherogenic biochemical abnormalities present in essential hypertension, added up as the cardiovascular metabolic syndrome. There are numerous reports of SNS overactivity in essential hypertension. Catecholamines may have metabolic hormonal effects at concentrations slightly above normal resting levels, and increased plasma catecholamines in hypertensive subjects may partly, or even fully, directly or indirectly, explain the metabolic disturbances constituting the cardiovascular metabolic syndrome. Because hypertensive subjects may respond to environmental stimuli with larger sympathoadrenal responses than normal subjects, and emotional stress has been associated with CAD, catecholamines may be the crucial link between stress and CVD. Environmental stress emanating from the workplace has been shown to activate the SNS. Thus, work stress may be considered a potential coronary risk factor.

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